AMENDMENTS

Amendments to the claims:

Please enter the amendments to claims 74, 75, 81, 97, 106, 109, 124, 129, 130, 162, 169 and 170, and cancel claims 76, 99, 100, 101, 116 and 131 as set forth in the complete listing of the claims that follows. This complete listing of the claims replaces previous claim listings.

1-73 (cancelled).

74 (currently amended). A method for determining the sequence in one or more sequence variations in a target nucleic acid, comprising:

(a) generating mass signals for target nucleic acid fragments and reference nucleic acid fragments by mass spectrometry, wherein the target nucleic acid fragments and the reference nucleic acid fragments result from [[one]] a specific cleavage of a target nucleic acid and a reference nucleic acid into fragments;

(b) identifying differences in the mass signals between target nucleic acid fragments and reference nucleic acid fragments, thereby identifying different fragments;

(c) generating one or more compomer witnesses corresponding to each different fragment identified in (b); [[and]]

(d) identifying a reduced set of candidate sequence variations corresponding to the compomer witnesses by determining sequence variations that would lead to the compomer witnesses, whereby the one or more sequence variations in the target nucleic acid are determined from the candidate sequence variations; and

(e) determining the sequence in the one or more sequence variations in the target nucleic acid from the reduced set of candidate sequence variations by an algorithm.

75 (currently amended). The method of claim 74, wherein the differences in mass signals in (b) are selected from the group consisting of missing signals, additional signals, signals that are different in intensity and signals having a different signal-to-noise ratio.

76 (cancelled).

77 (previous presented). The method of claim 74, wherein two or more sequence variations are determined.

78 (previous presented). The method of claim 74, wherein the sequence variation is at one or more base positions.

79 (previous presented). The method of claim 74, wherein the sequence variation is a mutation or a polymorphism.

80 (previous presented). The method of claim 79, wherein the mutation is an insertion, a deletion or a substitution.

81 (currently amended). The method of claim [[74]]79, wherein the polymorphism is a single nucleotide polymorphism.

82 (previous presented). The method of claim 74, wherein the target nucleic acid is from an organism selected from the group consisting of eukaryotes, prokaryotes and viruses.

83 (previously presented). The method of claim 82, wherein the organism is a bacterium.

84 (previously presented). The method of claim 83, wherein the bacterium is selected from the group consisting of Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sp (e.g. M. tuberculosis, M. avium, M. intracellulare, M. kansaii, M. gordonae), Staphylococcus aureus, Neisseria gonorrheae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus sp., Streptococcus faecalis, Streptococcus bovis, Streptococcus pneumoniae, Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus

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antracis, Corynebacterium diphtheriae, Corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringens, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides sp., Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira and Actinomyces israelli.

85 (previous presented). The method of claim 74, which further comprises (i) providing a target nucleic acid and a reference nucleic acid; (ii) generating fragments of the target nucleic acid and the reference nucleic acid by specific cleavage; and (iii) determining mass signals of the fragments, wherein the mass signals of (iii) are provided in (a).

86 (previous presented). The method of claim 85, wherein the target nucleic acid is in a mixture of nucleic acids.

87 (previous presented). The method of claim 85, wherein the mixture comprises the reference nucleic acid.

88 (previous presented). The method of claim 85, wherein the mixture comprises a plurality of reference nucleic acids.

89 (previous presented). The method of claim 85, wherein the mixture comprises a plurality of target nucleic acids.

90 (previous presented). The method of claim 85, wherein one specific cleavage agent is utilized to generate fragments.

91 (previous presented). The method of claim 85, wherein two or more specific cleavage agents are utilized to generate fragments.

92 (previous presented). The method of claim 85, wherein specific cleavage comprises treatment with an RNAse.

93 (previous presented). The method of claim 85, wherein specific cleavage comprises treatment with a specific cleavage agent selected from the group consisting of RNase T1, RNase U2, the RNase PhyM, RNase A, chicken liver RNase (RNase CL3) and cusavitin.

94 (previous presented). The method of claim 85, wherein specific cleavage comprises treatment with a glycosylase.

95 (previous presented). The method of claim 85, wherein the target nucleic acid is in a pool of nucleic acids from individuals.

96 (previous presented). The method of claim 85, wherein the target nucleic acid is genomic DNA from a single individual.

97 (currently amended). The method of claim 85, wherein the target nucleic acid is selected from the group consisting of single stranded DNA, double stranded DNA, cDNA, single stranded RNA, double stranded RNA, DNA/RNA hybrid, [[PNA]] and a DNA/RNA mosaic nucleic acid.

98 (previous presented). The method of claim 85, wherein the target nucleic acid is produced by transcription.

99 -101 (cancelled).

102 (previous presented). The method of claim 74, wherein sequence variations in the target biomolecule permit genotyping a subject, forensic analysis, disease diagnosis or disease prognosis.

103 (previous presented).   The method of claim 74, wherein the method determines epigenetic changes in a target nucleic acid molecule relative to a reference nucleic acid molecule.

104 (previous presented). The method of claim 74, wherein the target nucleic acid is from a tumor sample.

105 (previous presented). The method of claim 76, wherein compomer witnesses are generated based upon parameters selected from the group consisting of mass of the different fragment, peak separation between fragments whose masses differ by a single nucleotide in type or length, and mass spectrometer resolution.

106 (currently amended). The method of claim 74, wherein sequence variations in (d) are determined according to one or more ~~candidate sequences~~ candidate sequences having at most k sequence variations.

107 (previous presented). The method of claim 106, wherein k is one or two.

108 (previous presented). The method of claim 106, wherein k is three or more.

109 (currently amended). The method of claim 74, wherein the algorithm determines ~~further comprising: (e) scoring the candidate sequence variations, whereby a sequence variation in the target nucleic acid is determined from~~ the sequence in the one or more candidate sequence variations by scoring ~~in (e)~~.

110 (previous presented). The method of claim 109, wherein a simulated spectrum is generated for each sequence variation candidate, and each spectrum is scored.

111 (previous presented). The method of claim 109, wherein scores assigned to a sequence variation candidate for multiple target nucleic acids are combined for an overall score of the sequence variation candidate.

112 (previous presented). The method of claim 74, wherein sequence variation in the target nucleic acid is recorded in a record.

113 (previous presented). The method of claim 74, wherein the one or more compomer witnesses for each different fragment have a mass within a mass difference from the actual mass of the different fragment.

114 (previous presented). The method of claim 113, wherein the mass difference is the resolution of mass measurement.

115 (previously presented). A method for detecting one or more sequence variations in a target nucleic acid, comprising:

(a) generating mass signals for target nucleic acid fragments and reference nucleic acid fragments by mass spectrometry, where the target nucleic acid fragments and the reference nucleic acid fragments result from cleavage of a sample comprising a target nucleic acid by multiple cleavage reactions, wherein the target nucleic acid is in a nucleic acid mixture, and specific cleavage of a reference nucleic acid by the same cleavage reactions;

(b) identifying differences in the mass signals between the plurality of fragmentation patterns of target nucleic acid fragments and reference nucleic acid fragments, thereby identifying different fragments;

(c) identifying different fragments that are consistent with a particular sequence variation in the target nucleic acid;

(d) combining the consistent different fragments of (c) to obtain a spectrum of different fragments;

(e) generating from the spectrum of different fragments of (d) one or more compomer witnesses corresponding to each of the different fragments;

(f) determining sequence variations that are candidate sequences corresponding to the compomer witnesses;

(g) scoring the candidate sequences of (f); and

(h) determining one or more sequence variations in the target nucleic acid.

116 (cancelled).

117 (previous presented). The method of claim 115, wherein compomer witnesses are generated based upon parameters selected from the group consisting of mass of the different fragment, peak separation between fragments whose masses differ by a single nucleotide in type or length, and mass spectrometer resolution.

118 (previously presented). The method of claim 115, wherein sequence variations in (f) are determined according to one or more candidate sequences having at most k sequence variations.

119 (previous presented). The method of claim 118, wherein k is one or two.

120 (previous presented). The method of claim 118, wherein k is three or more.

121 (previous presented). The method of claim 115, wherein one or more sequence variations are recorded in a record.

122 (previous presented). The method of claim 115, wherein the one or more compomer witnesses for each different fragment have a mass within a mass difference from the actual mass of the different fragment.

123 (previous presented). The method of claim 122, wherein the mass difference is the resolution of mass measurement.

124 (currently amended). A method for detecting one or more sequence variations in a target nucleic acid, comprising:

(a) generating mass signals for target nucleic acid fragments and reference nucleic acid fragments by mass spectrometry and providing reference sequence s, a description of cleavage reaction conditions, a description of whether or not modified nucleotides are incorporated into all or part of the target sequence, a list of signals corresponding to different fragments between target nucleic acid fragments and reference nucleic acid fragments, and maximal sequence variation order k;

(b) generating one or more compomer witnesses c' corresponding to each different fragment identified in (a); [[and]]

(c) identifying a reduced set of candidate sequence variations corresponding to the compomer witnesses represented by $C_k := \{(c\,[\,i,\,j], b\,[\,i,\,j]: 1 \le i \le j \le$ length of s, and ord $[\,i,\,j] + \#b\,[\,i,\,j] \le k\}$, where C is a set of all bounded compomers within a string s, $c\,[\,i,\,j]$ is a compomer corresponding to substring $s\,[\,i,\,j]$, $b\,[\,i,\,j]$ is a boundary of the substring $s\,[\,i,\,j]$, ~~and whereby the one or more sequence variations in the target nucleic acid are determined from the candidate sequence variations~~; and

(d) detecting the one or more sequence variations in the target nucleic acid from the reduced set of candidate sequence variations by an algorithm.

125 (previously presented). The method of claim 124, wherein k is 1 or 2.

126 (previously presented). The method of claim 124, wherein k is 3.

127 (previously presented). The method of claim 124, wherein one or more sequence variations are recorded in a record.

128 (cancelled).

129. (currently amended). A method for determining one or more sequence variations in a target nucleic acid, comprising:

(a) generating mass signals for target nucleic acid fragments and reference nucleic acid fragments by mass spectrometry, where the target nucleic acid fragments and the reference nucleic acid fragments result from specific cleavage of a target nucleic acid and a reference nucleic acid into fragments;

(b) identifying differences in the mass signals between target nucleic acid fragments and reference nucleic acid fragments, thereby identifying different fragments;

(c) generating one or more compomer witnesses corresponding to each different fragment identified in (b); [[and]]

(d) identifying a reduced set of candidate sequence variations corresponding to the compomer witnesses represented by $C_k:=\{(c\,[\,i,\,j],\,b\,[\,i,\,j]:\,1\leq i\leq j\leq$ length of s, and ord $[\,i,\,j]\,+\,\#b\,[\,i,\,j]\leq k\}$, where C is a set of all bounded compomers within a string s, c $[\,i,\,j]$ is a compomer corresponding to substring s $[\,i,\,j]$, b $[\,i,\,j]$ is a boundary of the substring s $[\,i,\,j]$, ~~and whereby the one or more sequence variations in the target nucleic acid are determined from the candidate sequence variations~~; and

(e) identifying the one or more sequence variations in the target nucleic acid from the candidate sequence variations by an algorithm.

130 (currently amended). The method of claim 129, wherein the differences in mass signals in (b) are ~~selected from the group consisting of missing signals,~~ additional signals~~, signals that are different in intensity and signals having a different signal-to-noise ratio~~.

131-139 (cancelled).

140 (previously presented). The method of claim 129, which further comprises (i) providing a target nucleic acid and a reference nucleic acid; (ii) generating fragments of the target nucleic acid and the reference nucleic acid by specific cleavage; and (iii) determining mass signals of the fragments, wherein the mass signals of (iii) are provided in (a).

141-157 (cancelled).

158 (previously presented). The method of claim 131, wherein compomer witnesses are generated based upon parameters selected from the group consisting of mass of the different fragment, peak separation between fragments whose masses differ by a single nucleotide in type or length, and mass spectrometer resolution.

159-161 (cancelled).

162 (currently amended). The method of claim 129, <u>wherein the algorithm</u> <u>determines</u> ~~further comprising: (e) scoring the candidate sequence variations, whereby a~~ ~~sequence variation in the target nucleic acid is determined from~~ the <u>one or more</u> ~~candidate~~ sequence variation<u>s by</u> scoring ~~in (e)~~.

163 (cancelled).

164 (previously presented). The method of claim 162, wherein scores assigned to a sequence variation candidate for multiple target nucleic acids are combined for an overall score of the sequence variation candidate.

165-168 (cancelled).

169 (currently amended). A method for determining the sequence in one or more sequence variations in a target nucleic acid, comprising:

(a) generating mass signals for target nucleic acid fragments and reference nucleic acid fragments by mass spectrometry, where the target nucleic acid fragments and the reference nucleic acid fragments result from specific cleavage of a target nucleic acid and a reference nucleic acid into fragments;

(b) identifying differences in the mass signals between target nucleic acid fragments and reference nucleic acid fragments, thereby identifying different fragments;

(c) generating one or more compomer witnesses corresponding to each different fragment identified in (b);

(d) identifying a reduced set of candidate sequence variations corresponding to the compomer witnesses<u> by determining sequence variations that would lead to the compomer</u> <u>witnesses</u>~~, whereby the one or more sequence variations in the target nucleic acid are~~ ~~determined from the candidate sequence variations~~; and

(e) scoring the candidate sequence variations <u>in the reduced set</u>, whereby [[a]] <u>the</u> <u>sequence in the one or more</u> sequence variation<u>s</u> in the target nucleic acid [[is]] <u>are</u> determined from ~~the candidate sequence variation~~ scoring [[in (e)]].

170 (currently amended). The method of claim 169, wherein the differences in mass signals in (b) ~~are selected from the group consisting of missing signals,~~ additional signals~~, signals that are different in intensity and signals having a different signal-to-noise ratio~~.

171 (previously presented). The method of claim 169, which further comprises (i) providing a target nucleic acid and a reference nucleic acid; (ii) generating fragments of the target nucleic acid and the reference nucleic acid by specific cleavage; and (iii) determining mass signals of the fragments, wherein the mass signals of (iii) are provided in (a).

172 (previously presented). The method of claim 169, wherein a simulated spectrum is generated for each sequence variation candidate, and each spectrum is scored.

173 (previously presented). The method of claim 169, wherein scores assigned to a sequence variation candidate for multiple target nucleic acids are combined for an overall score of the sequence variation candidate.